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It is hereby certified that annexed here to is a true copy of **Application & Provisional Specification & Abstract** of the patent application as filed and detailed below:-

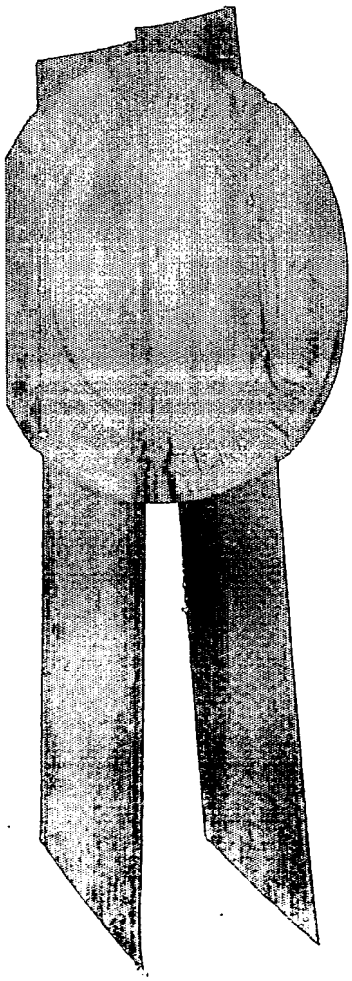
Date of application : **30-12-2003**

Application No : **1065/CHE/2003**

Applicants : **Dr. Reddys Laboratories Generics SBU an Indian Company having its registered office at 7-1-27, Ameerpet, Hyderabad – 500 016, A.P., India.**

In witness there of
I have here unto set my hand

Dated this the 1st day of March 2005
10th day of Phalgula, 1926(Saka)



By Authority of
THE CONTROLLER GENERAL OF PATENTS, DESIGNS AND TRADE MARKS.

M. S. V

(M.S.VENKATARAMAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

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Received Rs. ... in Cash - Cheque / M.O. / P.O. / D.D. dated 30.12.03 Vide C.B.R. No. 72114

FORM 1
THE PATENTS ACT, 1970
APPLICATION FOR GRANT OF A PATENT (Section 5(2), 7 and Rule 33A)

30/XII

We, Dr. Reddys Laboratory Generic SBU, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016 hereby declare

1. (a) that we are in possession of an invention titled "***Pharmaceutical compositions comprising acidic polymer sensitive active ingredients or pharmaceutical excipients and process of preparation thereof.***"
   (b) that the complete specification relating to this invention is filed with this application.
   (c) that there is no lawful ground of objection to the grant of a patent to us.
2. further declare that the inventors for the said invention are Raghupathi Kandarapu, Akhilesh Ashok Dixit, Vijay Dinanathji Nasare, and Mailatur Sivaraman Mohan.
   All citizens & residents of India belonging to Dr. Reddy's Laboratories Generics SBU, 7-1-27, AMEERPET, HYDERABAD - 500 016
3. that we are the assignee of the true and first inventors
4. that our address for service in India is as follows ;
   The General Manager,
   Research & Development,
   Dr. Reddy's Laboratories Ltd., Post Box No.15,
   Kukatpally, Hyderabad- 500 072, (A.P.) India
5. We, the true and first inventors for this invention declare that the applicant herein is our assignee

(Signed)_____
RAGHUPATHI KANDARAPU

(Signed)_____
AKHILESH DIXIT

(Signed)_____
VIJAY NASARE

(Signed)_____
M.S.MOHAN

1065/CHE/2003 30.12.2003

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application
7. following are the attachments with the application
   (a) provisional specification (11 pages, in triplicate, with Form 2)
   (b) abstract of the invention (01 page, in triplicate)
   (c) fee Rs. 3000.00 (three thousand rupees only) in bank draft bearing no 237876 dated 18.09.2003 drawn on HDFC bank.

We request that a patent may be granted to us for the said invention

Dated this Twenty sixth day of DECEMBER-2003

(Signed)_____
M.S.Mohan
General manager – R & D
Dr. Reddy's Laboratories, Generics

The Controller of Patents and Designs
Patent Office Branch, Chennai- 600 090.

FORM 2

THE PATENTS ACT 1970

PROVISIONAL SPECIFICATION

(SECTION 10)

1065/CHE/2003
30.12.03

PHARMACEUTICAL COMPOSITIONS COMPRISING ACIDIC POLYMER SENSITIVE ACTIVE INGREDIENTS OR PHARMACEUTICAL EXCIPIENTS AND PROCESS OF PREPARATION THEREOF

Dr. Reddys Laboratories, Generics

an Indian Company having its registered office at

7-1-27, Ameerpet
Hyderabad - 500 016, A.P., India

The following specification particularly describes the nature of this invention and the manner in which it is to be performed:

Pharmaceutical compositions comprising acidic polymer sensitive active ingredients or pharmaceutical excipients and process of preparation thereof

Field of Invention:

The present invention relates to the pharmaceutical compositions comprising active ingredients and pharmaceutically acceptable excipients, possessing an inherent tendency to chemically interact with acidic polymers, more preferably enteric coating material and to the process of manufacturing such compositions.

Background:

Acidic polymers consisting free carboxylic groups are widely used in pharmaceutical compositions, more particularly for enteric coating. Some of the acidic polymers are, but not limited to, Eudragit L 100, Shellac, polyvinyl acetate phthalate (PVAP), Cellulose acetate phthalate (CAP), Hydroxypropyl methylcellulose acetate phthalate (HPMCP), Hydroxypropyl methylcellulose acetate succinate (HPMCS). Development of enteric coated formulation, is hard met target in pharmaceutical industry. Usually the purpose of enteric coating the active ingredient is to prevent the degradation of the active ingredient in acidic conditions. Other application of enteric coat is to prolong the release of certain active ingredients through single day to a week. Under such circumstances, eventhough drug is well absorbed throughout the gastrointestinal tract the purpose of enteric coat is to delay the onset of absorption of active ingredient 1 to 2 hours relative to the immediate release formulations.

In certain cases enteric coating becomes more critical when active ingredient or excipients in a composition have a tendency to chemically interact with enteric coating materials and forms a slowly or even insoluble coating which retards the release of active ingredient. Tendency of active ingredient or excipients to chemically interact with the enteric coatings is a peculiarity exists in chemical structures thereof. Some widely used antidepressant agents such as Fluoxetine, Duloxetine, Nortryptylline Desipramine, Sertralline and Paroxetine are reported in prior art to interact with enteric coating materials and to form a slowly or even insoluble coating which retards the release.

Number of patents and research articles report the interaction of the carboxylic group of the enteric polymer and the amine group of the active or the excipient used in the formulation thereof.

Sarisuta N et al., prepared the films of various acidic polymers containing erythromycin and showed an amine salt interaction between the carboxyl group of the acid polymers and N-atom of erythromycin using NMR technique.

Takka S. et al., utilized the interaction between propranolol hydrochloride and anionic polymers to control the release of propranolol hydrochloride. The interaction between propranolol hydrochloride and anionic polymers were confirmed on the basis of UV difference spectra method.

Lee HK et al., observed that the polyanionic form of methacrylic acid:methacrylic acid methyl ester copolymer reacts readily with propranolol.HCl to give a sparingly soluble complex at saturation equilibrium. Propranolol: methacrylic acid copolymer complex is characterized by differential thermal analysis, and IR and UV spectroscopic methods. Propranolol content was found to be 68% in the complex. The value of the Hill coefficient (1.5) indicates that there is a high degree of positive cooperative interaction between propranolol and the polymer.

In past numerous approaches were developed to address the problem, one of the classic approach is to build the strong cementing layer or subcoat between enteric material and acid sensitive drug containing core, wherein interacting components are physically separated.

In all prior art references of enteric coated compositions comprising either acid susceptible or chemically interacting active ingredient or excipient a subcoat (a term interchangeable with cementing layer or intermediate layer or physical) is critical for the success of the invention. Water soluble or disintegrating or inert nature of subcoat was always an essential element of subcoat. Inert subcoat was used with an intention to prevent an interaction between active ingredient or excipient and the enteric coating material.

In the process of preventing the interaction between enteric coat and reactive components in core, water soluble subcoating materials were utilized to prevent any delay in release of drug in intestinal pH. Eventhough the scientists have managed to develop an enteric coated pharmaceutical composition of such active ingredient or excipients, the problem of chemical interaction or the chemistry involved in such interactions is still ill understood. Chemistry

involved in such interactions is required to be essentially studied to develop the formulation that will work totally on novel technique of stabilizing the drugs or excipients having a tendency to interact with enteric polymers. We have surprisingly found a common structural identity of active ingredients and excipients, which interacts with enteric coating polymers, to have a primary or secondary amino group in their structure. These amino groups are responsible for interaction with the free carboxylic groups of enteric coating polymer, resulting in relatively slow or even insoluble polymer. However, presence of amine groups may not be sole reason or interaction as few active ingredients which do not possess such a reactive group may also interact with enteric polymers in a same manner, but most of drugs represents or excipients this common structural identity of a primary amino acid in their structure. Finally this invention is directed towards the development of pharmaceutical compositions, wherein active ingredient or excipients has a tendency to interact with enteric coating, irrespective of its structure.

US patent No.5910319 discloses some means to prevent such chemical interactions, wherein the enteric material was neutralized with ammonia prior to use, moreover a sugar other than non-reducing sugar was incorporated in cement layer, alongwith water soluble polymer. The patent teaches neutralization of carboxylic groups in the enteric polymer at optimum level, whereby an interaction of active ingredient with enteric coating is prevented and still acid resistance of enteric coating was unaffected.

Use of subcoat is wellknown art, only the purpose may vary from product to product. US Patent No. 4786505, describes a method of preparing a stable formulation of Omeprazole, comprising a water-soluble intermediate coat layered on the core surface. The enteric coating is then layered over the water-soluble intermediate layer. US Patent No. 5035899, claims a formulation of acid labile bezimidazole derivatives, comprising subcoat of slightly water soluble film forming material and fine particles of a slightly water-soluble substance, suspended in the coating material.

In US patent 5035899, Saeki teaches the development of pharmaceutical composition by coating a core comprising a benzimidazole derivative using slightly water-soluble, film-forming material selected from the group consisting of ethyl cellulose and polyvinyl acetate and followed by enteric coat.

In accordance with the said invention we have found that the said interactions can be prevented without the neutralization of carboxylic group of enteric material prior to use, wherein the interactions are prevented only by use of novel subcoat alone. Unlike patent 5910319 the structural integrity of enteric polymer of developed formulation is unchanged, in order to maintain the desired acid resistance.

Objective of Invention:

Objective of present invention is to develop a stable pharmaceutical composition comprising active ingredients or excipients having tendency to interact with enteric coating material of the composition.

Another objective of present invention is to develop chemically reactive subcoat, to prevent abovesaid interactions in dissolution media or in gastrointestinal tract or during storage.

Another objective of present invention is to develop a subcoat comprising atleast one chemically reactive material and water soluble polymeric material.

Another objective of present invention is to develop a subcoat wherein chemically reactive component of subcoat is water soluble or water insoluble to prevent abovesaid interactions in dissolution media or in gastrointestinal tract or during storage.

One more objective of present invention is to develop the pharmaceutical composition without neutralizing the carboxylic groups of enteric polymer yet preventing the interaction between reactive drugs.

Another objective of invention is to develop a method of manufacturing such compositions.

Summary of Invention:

The present invention provides enteric coated pharmaceutical compositions comprising drug having a tendency to interact with enteric coating material. The pharmaceutical composition comprises:

a. A core comprising one or more drugs, with a tendency to interact with enteric coating material, one or more pharmaceutically acceptable excipients and optionally chemically active substance.
b. A subcoat or a intermediate layer, comprising atleast one chemically active substance or component
c. An enteric layer comprising a non-neutralised enteric coating material during coating process and a pharmaceutically acceptable excipient.
d. Optional finishing coat.

Detailed Description of Invention:

The present invention addresses inadequacies of prior art such as requirement of thick cement layer or subcoat and previously neutralized or neutralized enteric coated during process of polymer. For the discussion hereinafter the term "drug or active ingredient" stands for a therapeutic agent which possess inherent tendency to interact with enteric coating material and salt forms, freebase, solvates and hydrates thereof. In a specification following a term "chemically reactive substance" or "chemically reactive component" represents the material that undergoes competitive chemically reaction with carboxylic groups in the enteric coat to prevents the interaction between drug and enteric polymer. Chemically reactive substance defined hereinbefore present in either of the; core or a subcoat or in both of core and subcoat.

Description of Invention:

Composition of present invention, comprises (1) a core comprising one or more drugs with a tendency to interact with enteric coating material, optionally with a chemically reactive component (2) a chemically reactive subcoat over the core and (3) an enteric coating layered over the subcoat.

The Core:

Core is prepared by applying a drug-loaded layer to an inert core or it may be pellets comprising drug and atleast one pharmaceutical acceptable excipient. The core of said

invention comprises drug optionally with a chemically reactive substance. The core may be in form of pellets, granules, beads, minitablets and tablets. The core mentioned herein is prepared by the art wellknown to one ordinary skilled in the art.

The term 'core' incorporated herein refers to granules, pellets, minitablets, tablets and capsules that are conventionally used for oral administration. The abovesaid pellets can be prepared using extrusion and spheronisation or by coating non-pareil seeds or by melt pelletisation or by conventional pelletisation process. The most preferred non-pareil seeds are one prepared from starch and sucrose. Tablets and Minitablets can be prepared with or without involving a process of granulation. Conventional methods of granulation comprise wet granulation, dry granulation or melt granulation. The said core of a formulation is obtained by mixing active ingredient with fillers, surfactants, disintegrants, binders, lubricants and optionally a chemically reactive agent. The interactions between drug and enteric coat can also be prevented by use of chemically reactive agent alone in core, the percentage of chemically reactive agent may vary from about 1 to about 20 percent, preferably from about 2 to about 10 percent of the weight of core.

In general, the core comprise from about 10 to about 80 percent of the product, preferably from about 30 to about 70, more preferably from about 45 to about 65 percent of the product. The size of the cores depends, on the desired size of the pellet to be manufactured. In general, pellets should be of narrow particle size distribution. Core pellets thus prepared in accordance with the final pharmaceutical composition may be required to have particle size ranging from about 12 to 35 U.S. mesh, preferably from about 14 to 25 U.S. mesh, more preferably from about 14 to 20 U.S. mesh.

Subcoat or intermediate coat:

The basic purpose of subcoat is to prevent the interactions between the drug and enteric polymers and to provide a smooth base for the deposition of enteric layer. Novelty of said invention exists in subcoat, wherein the subcoat, unlike to the subcoat used in prior art references, is chemically reactive. Subcoat of said invention comprises a mixture of chemically reactive component and water soluble or water insoluble polymer, more preferably water soluble polymer. Subcoat of the present invention is chemically active and consists of an ingredient capable of rapidly reacting with carboxylic groups of enteric coat to

form the soluble amides and thus prevents the formation of insoluble amides of drug and enteric polymer, during dissolution. The chemically reactive agent utilised in subcoat, competes with drug to interact with enteric polymer. Chemically reactive agent prevents the interaction between drug and enteric polymer, due to its high affinity or reactivity for carboxylic groups in the enteric coat, compared to that of drug.

A water soluble subcoat comprises, any cellulosic polymer or derivative thereof widely used in pharmaceutical industry for the water soluble films. Some preferred water soluble polymers are, but not limited to polyvinylpyrrolidone hydroxypropyl methylcellulose, hydoxypropyl cellulose or the combinations thereof.

The chemically active material of subcoat which reacts with enteric material are basically amino acids, more preferably low molecular weight amino acids, more preferably glycine. Scope of term "chemically reactive substance" doesn't restricts to amino acids and may comprise all the substances which undergoes a chemical reaction with carboxylic groups of enteric coat by competing with active ingredient or interacting excipients.

Quantity of the subcoat applied while preparation of pharmaceutical compositions of said invention is generally 1 to 20 %, preferably 5 to 15%, more preferably 7 to 12 % of total weight of final composition. The amount of amino acid to be incorporated in subcoat is 10-30% more preferably 15-25 % of the subcoat on the weight basis.

A water insoluble subcoat that can used in one of the embodiments of the invention is Zein, available commercially as Zein F4000, Zein 6000 is basically a prolamine obtained from corn. The said subcoat may include antiadherant not limited talc alone, and other solid components, which are commonly used in manufacture of formulation.

In another preferred embodiment of invention, chemically reactive agent is distributed in core and subcoat, the total quantity of chemically reactive agent thus used 1 to 15 percent of total weight of product, more preferably 2 to 8 percent of total weight of product.

Enteric layer :

Enteric layer is an essential element of pharmaceutical composition developed herein, compatibility of enteric material is an important consideration for selection of enteric polymer. Anderson e.t al teaches (US patent 5910,319) an important limitation for the selection of enteric polymer. The polymer must be consisting only a small number of carboxylic acid groups per unit weight or repeating unit of polymer. Preferred enteric polymer was hydroxypropyl methylcellulose acetate succinate (HPMCAS), which contains not less than 4% and not more than 28% of succinyl group. Prior art suggests a critical limitation over the enteric coating polymer selection, wherein polymers with not less than 4% and not more than 28% of from core groups are preferred. Anderson proposed a method for better dissolution of enteric polymer, which provides sufficient acid resistance, and prevents interaction between enteric polymer and drug in intestinal condition. However, Anderson partially neutralizes the enteric polymer, using ammonia, preferably ammonium hydroxide. Further, Anderson sets two limitations, carboxylic content and partial neutralization of enteric polymer that are very critical for the success of invention.

The pharmaceutical composition developed in accordance with the said invention addresses this inadequacy of prior art, and facilitate the use of veriety of enteric polymer with carboxylic content, 2-4 times higher than Hydropropylmethyl cellulose acetate succinate.

We have developed a novel composition which overcomes these two limitations of prior art, and provides freedom for the use of enteric polymers with higher carboxylic groups and eventually without the need of neutralization of carboxylic group of enteric coat prior to the coat or during the coating.

Enteric coating may be applied from aqueous or organic solvent or as a powder, preferred method is to coat the subcoated pellets, granules , tablets , minitablets with solution of enteric polymer. The enteric coating layer is applied to the subcoated cores using conventional coating techniques such as pan coating or fluidized bed coating using solutions of polymers. The enteric coating polymers, thus used herein are, but not limited to, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, methacrylic acid and methacrylate copolymer, polyvinyl acetate phthalate. In the said oral pharmaceutical preparation of quantity of enteric coat varies from 5 to 30% of total weight of composition,

more preferably 10 to 25 percent of total weight of product. Commonly used plasticizers like Triethyl citrate and solid components like talc are also incorporated in enteric coating solution.

In a said invention "HPMCP" (hydroxypropyl methylcellulose phthalate), is a preferred enteric coating polymer. HPMCP has been demonstrated to be effective as enteric coating polymer by many researchers. It is widely used as an enteric coating agent by the pharmaceutical industry. "HPMCP" had been admitted into the USP/NF, EP AND JP. It dissolves at pH 5-5.5 and be controlled by varying the phthalyl content. Two types of different pH solubility, HP-55 and HP-50, are available. A suitable grade of "HPMCP" for a particular purpose should be selected in accordance with the properties and formulations.

HPMCP Enteric Coating Agent (Solvent System)

(Hypromellose Phthalate; USP/NF)

	Grade	Nominal Phthalyl Content	pH solubility in McIlvaine's Buffer Solution	Labeled Viscosity (cSt)*
HPMCP	50	24%	≧5.0	55
	55	31%	≧5.5	40
	55S			170

Note: * 10 wt.% in a mixture of equal weights of Methanol and Methylene Chloride according to the USP/NF measuring method.

Hydroxypropyl methylcellulose phthalate is preferred grade of HPMCP it is from Shin-Etsu Chemical Co. Ltd., Tokyo, Japan. Enteric coating solution is more preferably applied as solution of enteric polymer in organic solvents like acetone, dichloromethane and isopropyl alcohol, and combinations thereof. In another embodiment of invention suspension of enteric coated polymer may also be applied over the subcoat, provided the suspension remains homogenous. Application of the enteric layer to the subcoated product, using fluid bed type equipment (wherever preferable), or in a conventional pan coating with simultaneous spraying of enteric polymer solution or suspension and warm air drying. Temperature of the drying air and the temperature of the circulating mass of pellets should be kept in the ranges advised by the manufacturer of the enteric polymer. A finishing layer over the enteric layer is not necessary in every case, but improves the elegance of the product and its handling, storage and machinability and may provide further benefits as well. The simplest finishing

layer is simply a small amount, about less than 1% of an anti-static ingredient such as talc or silicon dioxide, simply dusted on the surface of the pellets.

Enteric coated composition of present invention, shows acid resistance in gastric conditions at 37C, after two hours the quantity of active ingredient released in gastric media was found below 10%, while the same composition in buffer solution of pH 6.8 maintained at temperature 37 C, in USP dissolution apparatus released not less than 80% of active ingredient after 10-30 minutes.

Following are given few examples of pharmaceutical compositions of active ingredients sensitive to enteric polymers which do not limits the scope of an invention and only presented here to show how the invention be carried out. The example represents preferred embodiments of the invention.

Example 1:

Composition and Manufacturing Details of Fluoxetine Delayed Release Capsules

1. Composition:

Name of the Ingredient	Functional Category	Quantity/Capsule
CORE PELLETS		
Fluoxetine HCl	Active agent	101.0
Avicel PH 105	Filler or Diluent	7.5
Mannitol USP	Filler or Diluent	212.7
Glycine	Stabilizer	20.0
Sodium lauryl sulfate	Solubilizer	11.3
Aerosil	Dispersing aid	7.5
Copovidone (Plasdone S-630)	Binder	15.0
Purified water	solvent	q.s.
Core weight		375.0
SUB-COATING		
Copovidone (Plasdone S-630)	Sub-coating polymer	20.0
Glycine	Stabilizer	10.0
Talc	Anti-adherent	5.0
Purified water	solvent	Q.S.
Sub-coat weight		35.0
ENTERIC-COATING		
HPMC-P HP-55	Enteric polymer	94.2
Triethyl citrate	Plasticizer	9.4
Talc	Anti-adherent	14.1
Isopropyl alcohol	Solvent	q.s.
Dichloromethylene	Solvent	q.s.
Enteric-coat weight		117.7

2. Method of Manufacture:

A) Preparation of core pellets using Extruder-Spheronizer

i) Weigh all the ingredients listed in the composition of core (except Copovidone), take in a polyethylene bag of suitable size and mix for 5 minuets.

ii) Pass the blend through mesh # 40.

iii) Load the sifted blend into a double cone blender and mix for 15 minutes.

iv) Dissolve copovidone in suitable amount of water (water quantity depends on the batch size) and use as a granulating fluid.

v) Using copovidone-granulating fluid, granulate the blend. Continue the granulation process till wet mass suitable for extrusion-spheronization is obtained.

vi) Subject the wet-mass for extrusion-spheronization process to produce the pellets.

vii) Dry the pellets at 65°C for 3 hours in a tray drier.

viii) After drying, collect the pellets of sieve fraction #14/20 and use for coating.

B) Sub-coating with Plasdone-630

i) Dissolve the ingredients of sub-coating formula in water (quantity depends on the batch size) and use as a coating fluid.

ii) Load the pellets in a Neocota and perform the sub-coating.

iii) Continue the sub-coating process till 9-10% w/w weight gain takes place.

C) Enteric-coating with HPMC-P HP-55 and filling in the capsules

i) Perform the enteric coating on sub-coated pellets.

ii) Prepare the enteric-coating fluid by dissolving the ingredients listed in enteric composition using isopropyl alcohol and dichloromethane (1:1) as a solvent.

iii) Load the sub-coated pellets in Neocota and coat till approximately 23-25% weight gain occurs.

iv) After coating process is over, blend the enteric coated pellets with 1% w/w Talc and fill in the capsules (0'elongated).

Abstract:

Present invention provides pharmaceutical compositions comprising one or more active ingredient and/or pharmaceutically acceptable excipient having tendency to interact with carboxylic group consisting acidic polymers, more particularly enteric coating material and at least one chemically reactive component as an essential component of composition.

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